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NEURO-FUZZY SYSTEM FOR PROSTATE CANCER DIAGNOSIS

LUIGI BENECCHI

ABSTRACT

Objectives. To develop a neuro-fuzzy system to predict the presence of prostate cancer. Neuro-fuzzy systems harness the power of two paradigms: fuzzy logic and artificial neural networks. We compared the predictive accuracy of our neuro-fuzzy system with that obtained by total prostate-specific antigen (tPSA) and percent free PSA (%fPSA).

Methods. The data from 1030 men (both outpatients and hospitalized patients) were used. All men had a tPSA level of less than 20 ng/mL. Of the 1030 men, 195 (18.9%) had prostate cancer. A neuro-fuzzy system was developed using the coactive neuro-fuzzy inference system model.

Results. The mean area under the receiver operating characteristic curve for the neuro-fuzzy system output was 0.799 ± 0.029 (95% confidence interval 0.760 to 0.835), for tPSA, it was 0.724 ± 0.032 (95% confidence interval 0.681 to 0.765), and for %fPSA, 0.766 ± 0.024 (95% confidence interval 0.725 to 0.804). Furthermore, pairwise comparison of the area under the curves evidenced differences among %fPSA, tPSA, and neuro-fuzzy system's output (tPSA versus neuro-fuzzy system's output, $P = 0.008$; %fPSA versus neuro-fuzzy system's output, $P = 0.032$). The comparison at 95% sensitivity showed that the neuro-fuzzy system had the best specificity (31.9%).

Conclusions. This study presented a neuro-fuzzy system based on both serum data (tPSA and %fPSA) and clinical data (age) to enhance the performance of tPSA to discriminate prostate cancer. The predictive accuracy of the neuro-fuzzy system was superior to that of tPSA and %fPSA. UROLOGY **68:** 357–361, 2006. © 2006 Elsevier Inc.

Prostate cancer is the second most common cause of cancer death among men in most industrialized countries.[1] Intracapsular prostate cancer is curable and can be detected by screening with total prostate-specific antigen (tPSA).[1] Furthermore, only 30% of men with an elevated serum tPSA concentration (4 ng/mL or greater) have prostate cancer on biopsy.[1,2] Various techniques such as PSA density and transition zone density may enhance the accuracy of the PSA test. Measurement of the percentage of free PSA (%fPSA) or complex PSA of the total serum PSA concentration has also been shown to reduce the false-positive PSA results by 20% to 40%.[3,4] The probability of prostate cancer can be estimated by logistic regression analysis[5–7] and artificial neural networks (ANNs),[8,9] which can be trained to predict diagnostic outcomes. However, none of those tools has resolved the problem of low specificity for prostate cancer diagnosis.

Where uncertainty exists such as in the medical field, fuzzy logic could play an important role in making decisions. Fuzzy logic is the science of reasoning, thinking, and inference that recognizes and uses the real world phenomenon that everything is a matter of degree. In the simplest terms, fuzzy logic theory is an extension of binary theory that does not use crisp definitions and distinctions.[10] Instead of assuming everything must be defined crisply into black and white (binary view), fuzzy logic is a method that captures and uses the concept of fuzziness in a computationally effective manner. This concept was developed 40 years ago when Lotfti Zadeh (as referenced by Dubois and Prade[10] and Kuncheva and Steimann[11]), originally an engineer and systems scientist, expressed the concern that as the complexity of a system increased, the information afforded by traditional mathematical models rapidly declined. Using a fuzzy approach, the transition between terms can

From the Department of Urology, Fidenza Hospital, Parma, Italy

Reprint requests: Luigi Benecchi, M.D., Department of Urology, Fidenza Hospital, Via Vaio 1 Fidenza, Parma 43010, Italy. E-mail: benecchi.luigi@libero.it

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TABLE I. *Patient characteristics*

Parameter	All	Controls	Prostate Cancer	*P* Value (*t* Test)
Patients (n)	1030	835	195	
Age (yr)	67.7 (45–92.7)	67.89 (45–92.7)	67.18 (48.8–86.3)	0.99
tPSA (ng/mL)	5.54 (0.12–19.9)	5.03 (0.12–19.9)	7.89 (1.2–19.8)	<0.001
fPSA (ng/mL)	0.88 (0.033–7.88)	0.89 (0.03–6.14)	0.86 (0.24–7.8)	0.54
%fPSA	18.6 (3.27–65)	20.18 (4.05–65)	11.7 (3.26–44.5)	<0.001
PSA density	0.137 (0.005–0.896)	0.121 (0.005–0.566)	0.22 (0.062–0.896)	<0.001
Transition zone PSA density	0.249 (0.013–1.64)	0.23 (0.017–1.45)	0.44 (0.013–1.64)	<0.001

KEY: tPSA = total prostate-specific antigen; fPSA = free PSA; %fPSA = percentage of free PSA.
Data presented as median, with range in parentheses.

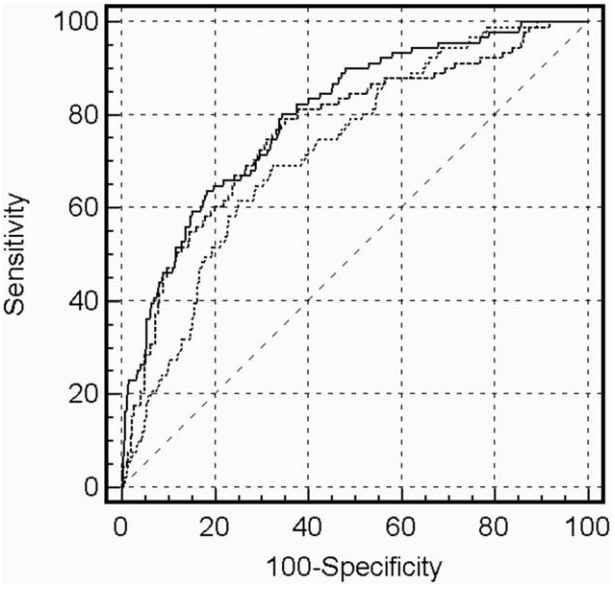

FIGURE 1. *Receiver operating characteristic curves for neuro-fuzzy system (solid line), tPSA (dotted line), and %fPSA (dashed line).*

be gradual, and the binary, or all or none, options become the extreme ends of a continuum. The fuzzy view of the world was put into operation for computational purposes through the use of the fuzzy set.[12,13] Variables, variable terms, and definitions can be thought of in terms of sets and set theory. In traditional set theory, using the binary view, something either belongs to a set or does not, depending on whether it fits the definition for that set. Thus, it has a degree of membership (μ) to the set either equal to 1 ($\mu = 1$) or equal to 0 ($\mu = 0$). In fuzzy set theory, something can partially belong to a set. A value for a variable might partially belong to a set and have a degree of membership anywhere between 0 and 1 (ie, $0 < \mu < 1$) and thus could partially belong to several sets with the total membership equaling 1.[14,15]

Neuro-fuzzy systems are fuzzy systems that use ANN theory to determine their properties (fuzzy sets and fuzzy rules) by processing data samples. Neuro-fuzzy systems harness the power of the two paradigms: fuzzy logic and ANNs, by using the mathematical properties of ANNs in tuning rule-based fuzzy systems that approximate the way humans process information. A specific approach in neuro-fuzzy development is the neuro-fuzzy inference system, which has shown significant results in modeling nonlinear functions. In a neuro-fuzzy inference system, the membership function parameters are extracted from a data set that describes the system behavior. The neuro-fuzzy inference system learns features in the data set and adjusts the system parameters according to a given error criterion.[13,14] Successful implementations of the neuro-fuzzy inference system in biomedical engineering have been reported for classification and data analysis.[16–18]

The aim of our study was to develop a neuro-fuzzy system to predict the presence of prostate cancer. We compared the predictive accuracy of this neuro-fuzzy system with that obtained by tPSA and %fPSA. To our knowledge, this is the first study using a neuro-fuzzy system for prostate cancer diagnosis.

MATERIAL AND METHODS

We retrospectively reviewed from our database male patients (both outpatients and hospitalized patients) who underwent tPSA and fPSA assay from January 2002 to September 2005. This population did not represent a screening population, but patients with urologic symptoms referred to the urology practice for treatment of a genitourinary disorder or for a checkup. From January 2002 to August 2003, systematic sextant biopsies using transrectal ultrasonography were performed in patients with positive or doubtful digital rectal examination (DRE) findings, as well as in those with a tPSA level greater than 4 μg/L and %fPSA less than 22%. From September 2003 to September 2005, systematic 12 or 14-core biopsies were performed in patients with a tPSA level greater than 3 μg/L and %fPSA less than 22%. Serum was obtained before any diagnostic procedure. Both tPSA and fPSA were assayed using the chemiluminescent immunoassay Immulite (Diagnostic Products), according to the manufacturer's instructions. The assays are solid-phase, two-site, sequential chemiluminescent immunometric tests that are performed automatically on an automated analyzer with a detection limit of 0.02 and 0.03 μg/L, respectively, for fPSA and tPSA.

The inclusion criteria were age older than 45 years and no history of prostate cancer. All men underwent a detailed clinical examination that included DRE and serum tPSA and fPSA

TABLE II. *Validation group: cutoff and specificity at 95% and 90% of sensitivity*

	Cutoff for 95% Sensitivity	Cutoff for 90% Sensitivity	AUC ± SD (95% CI)
fPSA (ng/mL)	3.2 (26% specificity)	3.9 (35.5% specificity)	0.724 ± 0.032 (0.681–0.765)
%fPSA	29 (14% specificity)	23.7 (30.9% specificity)	0.766 ± 0.024 (0.725–0.804)
Logistic regression	0.0626 (24.7% specificity)	0.0973 (39.2% specificity)	0.783 ± 0.030 (0.743–0.820)
Neuro-fuzzy system	0.07 (31.9% specificity)	0.13 (52% specificity)	0.799 ± 0.029 (0.760–0.835)

KEY: AUC = area under curve; CI = confidence interval; other abbreviations as in Table I.

determinations. Patients were excluded from analysis because of concomitant finasteride treatment, a tPSA level greater than 20 ng/mL, or recent urethral catheterization, which may distort the tPSA value. Patients who rejected a proposed prostatic biopsy were excluded. All patients with prostate carcinoma were diagnosed histopathologically. After applying these study inclusion and exclusion criteria, our initial sample of 2850 patients was decreased to 1030. All the men were white.

The 1030 men were randomly divided into four groups: training group (n = 463 [45%]), cross-validation group (n = 52 [5%]), test group (n = 52 [5%]), and validation group (n = 463 [45%]).

A fuzzy neural network was developed using the coactive neuro-fuzzy inference system model, which integrates adaptable fuzzy inputs with a modular neural network to approximate complex functions rapidly and accurately. The coactive neuro-fuzzy inference system model optimizes the fuzzy rules (membership function parameters) with back-propagation, so human knowledge is not required.

The fuzzy control method used was the Takagi-Sugeno-Kang, and each input was specified to consist of five bell-shaped membership functions. The number of training epochs was 1000.

Cross validation is a method for stopping network training. This method monitors the error on an independent set of data and stops training when this error begins to increase. This is considered to be the point of best generalization. The best weights of the network are automatically saved at the point at which the cross-validation error is at its lowest point. When testing the network, these best weights are loaded into the network, after the testing set is fed into the network and the network output is compared with the desired output. Data from the training group were used to train the ANN, which was composed of an input layer with three neurons (preprocessed values of tPSA, %fPSA, and age), a hidden layer with hidden neurons, and an output layer with one neuron representing the output value of the predictor, which is a measure of the probability of prostate cancer. The predictive variables were tPSA, %fPSA, and age; all variables were considered as continuous variables.

This trained and tested neural network was validated with the inputs of the last 463 cases (45%), so the obtained output values were compared with the real presence or absence of prostate cancer.

The software tool used to obtain the results presented in this report can be found on our server: http://www.urologiaparma.com/neurofuzzy.htm.

The ANN model was compared with a multivariate logistic regression analysis of the parameters used as input variables to the ANN. In the logistic model, the coefficients were determined from the training and test sets; the validation set was used to verify the generalization of the regression. The forward stepwise model was used. Age was excluded from the final model when the forward selection procedure was applied. The best fit of the logistic regression analysis models was tested by the Hosmer-Lemeshow test.

The variables of the different groups were compared using the t test, with $P < 0.05$ considered significant. The receiver operating characteristic curve was generated by plotting sensitivity versus 1 − specificity, and the area under the curve was calculated and compared.

RESULTS

Table I lists the descriptive statistics of the 1030 patients. Their median age was 67.7 years (range 45 to 92), and 195 patients (18.9%) had prostate cancer.

The mean area under the receiver operating characteristic curve for the ANN output was 0.799 ± 0.029 (95% confidence interval [CI] 0.760 to 0.835), for logistic regression analysis, it was 0.783 ± 0.030 (95% CI 0.743 to 0.820), for tPSA was 0.724 ± 0.032 (95% CI 0.681 to 0.765), and for %fPSA was 0.766 ± 0.024 (95% CI 0.725 to 0.804) (Fig. 1). Furthermore, a comparison of the areas under the curve evidenced differences among %fPSA, tPSA and ANN output that were statistically significant (tPSA versus ANN, $P = 0.008$; %fPSA versus ANN, $P = 0.032$). No difference was found between the area under the curve for logistic regression analysis and %fPSA ($P = 0.14$).

Using the receiver operating characteristic analysis, the ANN output cutoff value for a best discrimination between prostate cancer cases and controls was 0.19, corresponding to 71.4% sensitivity, 69.3% specificity, and a positive likelihood ratio of 2.35. The value of 0.07 for ANN output corresponded to 95% sensitivity and 31.9% specificity. The tPSA cutoff of 3.2 ng/mL corresponded to 95% sensitivity and 26% specificity (Table II). The specificity of %fPSA was the lowest at 90% and 95% sensitivity, because the evaluation of %fPSA was done for all of the tPSA range and not only in the tPSA gray zone (Table II).

COMMENT

The diagnostic tests currently used for early prostate carcinoma detection are fraught with a considerable number of false-positive and false-negative results.[1,19] The determination of %fPSA[20,21] and the concept of PSA density and PSA transition zone density[22] have been included in the diagnostic workup for prostate carcinoma. However, none of those tools has resolved the problem of low specificity for prostate cancer diagnosis.[23] Several statis-

tical methods such as Cox proportional hazards and logistic regression analysis have been used to study the probability of having prostate carcinoma,[5,6,24] but ANNs have the ability to predict the outcome for an individual patient in a way that is not possible with conventional statistics.[24] Recent studies have evaluated the application of ANNs to the diagnosis of prostate carcinoma.[25,26] Snow *et al.*[9] reported the first results in 1994. Since then, several studies have been performed using ANNs or conventional algorithms to enhance the detection of prostatic carcinoma.[25–28] In 1998, Carlson *et al.*[6] introduced a logistic regression model that included %fPSA, tPSA, and patient age. They found an 11% increase in specificity compared with the use of %fPSA alone within the 4 to 20-μg/L tPSA range.[6] Virtanen *et al.*[24] used another logistic regression model and an ANN incorporating %fPSA, tPSA, DRE status, and heredity factor at a tPSA level of 3 to 10 μg/L. The results provided better diagnostic accuracy for prostate cancer detection, with %PSA and DRE status as the most powerful predictors. A large multicenter evaluation of an ANN with five variables (tPSA, %fPSA, patient age, prostate volume, and DRE status) demonstrated an enhanced accuracy of prostate cancer detection with a reduction in unnecessary biopsies.[29]

The proposed neuro-fuzzy system can be used with a wide range of PSA (0 to 20 ng/mL). Another advantage of this neuro-fuzzy system is the reduced number of input variables. It only requires tPSA, %fPSA, and age. The absence of prostate volume offers greater use because an ultrasound scan to measure the prostate volume is not necessary. The main aim of our study, however, was to establish a clinically usable program for the individual calculation of prostate cancer risk. Using a simple ANN with limited input variables (tPSA, %fPSA, and age), we demonstrated significantly better performance for the neuro-fuzzy system output than for tPSA and %fPSA in enhancing the specificity and sensitivity.

CONCLUSIONS

This report presented a neuro-fuzzy system that used both serum data (tPSA and %fPSA) and clinical data (patient age) to enhance the performance of tPSA to discriminate prostate cancer. The predictive accuracy of the neuro-fuzzy system was superior to that of tPSA and %fPSA. The proposed neuro-fuzzy system combined the neural network adaptive capabilities and the fuzzy logic qualitative approach.

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